Patent Application
Docket No.: 25808A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

In re Application of: CARPINO, PHILIP A.	
	Group Art Unit: 1625
Serial No.: 10/823,152 Filed: April 12, 2004	Examiner: DESAI, RITA J
For: CANNABINOID RECEPTOR LIGANDS AND USES THEREOF	

APPEAL BRIEF

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

This is an appeal from an advisory action mailed on September 4, 2008 and an Office Action mailed on August 4, 2008, finally rejecting claims 1, 4, 8-11, 31, 35, 36, 42, 43, 49, 55, 59 and 64, all the claims remaining in the Application. A notice of Appeal was filed and received in the USPTO on September 8, 2008.

Please charge to Deposit Account No.16-1445 the $510.00 to cover the fee for the appeal and any additional fees or adjustments to the fee for the appeal.

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REAL PARTY IN INTEREST

This Application is assigned to Pfizer Inc., a U.S. Corporation organized under the laws of the State of Delaware and having its headquarters at 235 East 42nd Street, New York, New York USA.

RELATED INTERFERENCES AND APPEALS

The subject matter of this Appeal is not related to any co-pending Interferences or Appeals in the U.S. Patent & Trademark Office.

STATUS OF CLAIMS

1. Claims 1, 4, 8-11, 31, 35, 36, 42, 43, 49, 55, 59 and 64 remain in the application.

2. Claims 5-6, 12-29, 32-33, 37-41, 44-48, 50-54 and 56-58 were previously cancelled in response to a restriction requirement.

3. Claims 2-3, 7, 12-30, 34, 37-41, 60-63, and 65-73 were previously canceled without prejudice or without admitting anticipation or obviousness.

4. Claims 1, 4, 8-11, 31, 35, 36, 42, 43, 49, 55, 59 and 64 have been finally rejected under 35 U.S.C. §112, first paragraph for non-enablement over the scope of the claims.

5. Claims 1, 4, 8-11, 31, 35, 36, 42, 43, 49, 55, 59 and 64 have been finally rejected on the ground of non-statutory obviousness-type double patenting over Claims 1-23 of US Patent No. 7,230,024.

6. No claims have been allowed.

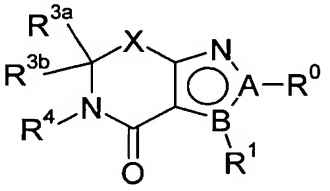
7. Claims 1, 4, 8-11, 31, 35, 36, 42, 43, 49, 55, 59 and 64 are being appealed.

STATUS OF AMENDMENTS

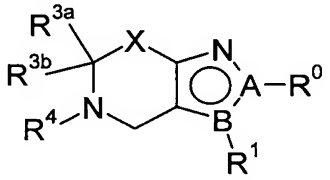
All amendments in this Application have been entered without objection.

SUMMARY OF CLAIMED SUBJECT MATTER

The present invention provides compounds of Formula (I) or (II) that act as cannabinoid receptor ligands (in particular, CB1 receptor antagonists)



(I)



(II)

wherein

A is nitrogen and B is carbon, or A is carbon and B is nitrogen;

R^0 is an aryl optionally substituted with one or more substituents, or a heteroaryl optionally substituted with one or more substituents (preferably, R^0 is a substituted phenyl, more preferably a phenyl substituted with one to three substituents independently selected from the group consisting of halo (preferably, chloro or fluoro), $(C_1$-$C_4)$alkoxy, $(C_1$-$C_4)$alkyl, halo-substituted $(C_1$-$C_4)$alkyl (preferably fluoro-substituted alkyl), and cyano, most preferably, R^0 is 2-chlorophenyl, 2-fluorophenyl, 2,4-dichlorophenyl, 2-fluoro-4-chlorophenyl, 2-chloro-4-fluorophenyl, or 2,4-difluorophenyl);

R^1 is aryl optionally substituted with one or more substituents, heteroaryl optionally substituted with one or more substituents, $-CH=CH-R^{1a}$, or $-CH_2CH_2-R^{1a}$, where R^{1a} is hydrogen or a chemical moiety selected from $(C_1$-$C_8)$alkyl, 3- to 8-membered partially or fully saturated carbocyclic ring(s), 3- to 6-membered partially or fully saturated heterocycle, aryl, heteroaryl, where the chemical moiety is optionally substituted with one or more substituents;

X is a bond or $-C(R^{2a})(R^{2b})$, where R^{2a} and R^{2b} are each independently hydrogen, $(C_1$-$C_4)$alkyl, or halo-substituted $(C_1$-$C_4)$alkyl (preferably, R^{2a} and R^{2b} are both hydrogen);

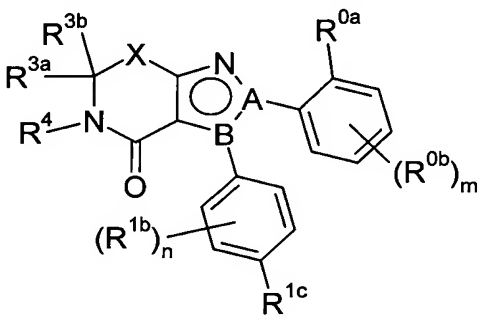
R^{3a} and R^{3b} are each independently hydrogen, $(C_1$-$C_4)$alkyl, or halo-substituted $(C_1$-$C_4)$alkyl; and

R^4 is a chemical moiety selected from the group consisting of $(C_1$-$C_8)$alkyl, aryl, heteroaryl, aryl$(C_1$-$C_4)$alkyl, a 3- to 8-membered partially or fully saturated carbocyclic ring(s), heteroaryl$(C_1$-$C_3)$alkyl, 5-6 membered lactone, 5- to 6-membered lactam, and a 3- to 8-membered partially or fully saturated heterocycle, where said chemical moiety is optionally substituted with one or more substituents;

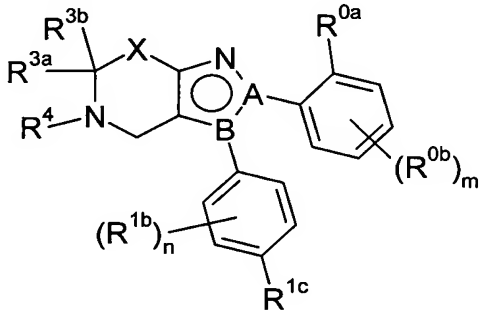
a pharmaceutically acceptable salt thereof, a prodrug of the compound or the salt, or a solvate or hydrate of the compound, the salt or the prodrug;

provided that when the compound is a compound of Formula (II), R^{3a} and R^{3b} are not both hydrogen when X is a bond. **(page 3, line 17 through page 4, line 20; and Original Claim 1)**

The present invention also provides a preferred embodiment of the present invention, in Claim 42 and its dependent claims, a compound of Formula (III) or (IV).



(III)



(IV)

wherein

A, B, X, R^{2a}, R^{2b}, R^{3a}, R^{3b} and R^4 are as defined above;

R^{0a}, R^{0b}, R^{1b}, and R^{1c} are each independently halo, $(C_1\text{-}C_4)$alkoxy, $(C_1\text{-}C_4)$alkyl, halo-substituted $(C_1\text{-}C_4)$alkyl, or cyano; and

n and m are each independently 0, 1 or 2;

a pharmaceutically acceptable salt thereof, a prodrug of the compound or the salt, or a solvate or hydrate of the compound, the salt or the prodrug:

provided that when the compound is a compound of Formula (IV), R^{3a} and R^{3b} are not both hydrogen when X is a bond. **(page 4, line 21 through page 5, line 7; and Original Claim 42)**

In preferred embodiments of the present invention, R^4 is a chemical moiety selected from the group consisting of $(C_1\text{-}C_8)$alkyl, aryl$(C_1\text{-}C_4)$alkyl, 3- to 8-membered partially or fully saturated carbocyclic ring(s), and 3- to 8-membered partially or fully saturated heterocycle, where said chemical moiety is optionally substituted with one or more substituent. **(page 5, lines 8-12 and Original Claim 2)**

More preferably, R^4 is $(C_1\text{-}C_8)$alkyl, halo-substituted $(C_1\text{-}C_8)$alkyl (preferably, fluoro-substituted $(C_1\text{-}C_8)$alkyl), cyclopentyl, cyclohexyl, piperidin-1-yl, pyrrolidin-1-yl, or morpholin-1-yl. **(page 5, lines 13-15 and Original Claim 3)**

Preferably, R^0 and R^1 are each independently a phenyl substituted with 1 to 3 substituents independently selected from the group consisting of halo, (C_1-C_4)alkoxy, (C_1-C_4)alkyl, halo-substituted (C_1-C_4)alkyl, and cyano; **(page 5, lines 16-18; and Original Claim 7)**

More preferably, R^0 and R^1 are each independently a phenyl substituted with 1 to 2 substituents independently selected from the group consisting of chloro, fluoro, (C_1-C_4)alkoxy, (C_1-C_4)alkyl, fluoro-substituted (C_1-C_4)alkyl), and cyano; **(page 5, lines 19-21; and Original Claim 8)**

Most preferably, R^0 is 2-chlorophenyl, 2-fluorophenyl, 2,4-dichlorophenyl, 2-fluoro-4-chlorophenyl, 2-chloro-4-fluorophenyl, or 2,4-difluorophenyl; and R^1 is 4-chlorophenyl, 4-cyanophenyl or 4-fluorophenyl. **(page 5, lines 22-24; and Original Claim 9)**

Preferred compounds having Formula (I), where A is nitrogen, B is carbon, and X is a bond include: 2-(2-chloro-phenyl)-5-isopropyl-3-(4-methoxy-phenyl)-5,6-dihydro-2H-pyrrolo[3,4-c]pyrazol-4-one; 2-(2-chloro-phenyl)-5-isopropyl-3-(4-cyano-phenyl)-5,6-dihydro-2H-pyrrolo[3,4-c]pyrazol-4-one; 3-(4-chloro-phenyl)-2-(2-chloro-phenyl)-5-(2,2,2-trifluoro-ethyl)-5,6-dihydro-2H-pyrrolo[3,4-c]pyrazol-4-one; 3-(4-chloro-phenyl)-2-(2-chloro-phenyl)-5-cyclohexyl-5,6-dihydro-2H-pyrrolo[3,4-c]pyrazol-4-one; 3-(4-chloro-phenyl)-2-(2,4-dichloro-phenyl)-5-isopropyl-5,6-dihydro-2H-pyrrolo[3,4-c]pyrazol-4-one; 3-(4-chloro-phenyl)-2-(2,4-dichloro-phenyl)-5-(2,2,2-trifluoro-ethyl)-5,6-dihydro-2H-pyrrolo[3,4-c]pyrazol-4-one; 3-(4-chloro-phenyl)-5-cyclohexyl-2-(2,4-dichloro-phenyl)-5,6-dihydro-2H-pyrrolo[3,4-c]pyrazol-4-one; 3-(4-chloro-phenyl)-2-(3-chloro-phenyl)-5-isopropyl-5,6-dihydro-2H-pyrrolo[3,4-c]pyrazol-4-one; 3-(4-cyano-phenyl)-2-(3-chloro-phenyl)-5-(2,2,2-trifluoro-ethyl)-5,6-dihydro-2H-pyrrolo[3,4-c]pyrazol-4-one; 2-(2-chloro-phenyl)-5-isopropyl-3-(4-chloro-phenyl)-5,6-dihydro-2H-pyrrolo[3,4-c]pyrazol-4-on; 3-(4-chloro-phenyl)-2-(3-chloro-phenyl)-5-(2,2,2-trifluoro-ethyl)-5,6-dihydro-2H-pyrrolo[3,4-c]pyrazol-4-one; and 3-(4-chloro-phenyl)-2-(3-chloro-phenyl)-5-cyclohexyl-5,6-dihydro-2H-pyrrolo[3,4-c]pyrazol-4-one; a pharmaceutically acceptable salt thereof, or a solvate or hydrate of said compound or said salt. **(page 5, line 25 through page 6, line 8; and Original Claim 10)**

More preferred compounds include: 2-(2-chloro-phenyl)-5-isopropyl-3-(4-cyano-phenyl)-5,6-dihydro-2H-pyrrolo[3,4-c]pyrazol-4-one; 2-(2-chloro-phenyl)-5-isopropyl-3-(4-chloro-phenyl)-5,6-dihydro-2H-pyrrolo[3,4-c]pyrazol-4-one; and 3-(4-chloro-phenyl)-2-(2-chloro-phenyl)-5-(2,2,2-trifluoro-ethyl)-5,6-dihydro-2H-pyrrolo[3,4-c]pyrazol-4-one; a pharmaceutically acceptable salt thereof, or a solvate or hydrate of said compound or said salt. **(page 6, lines 9-14; and Claim 11)**

Compounds of the present invention have been shown to be useful cannabinoid receptor ligands (in particular, CB1 receptor antagonists). Accordingly, another aspect of the present invention is a pharmaceutical composition that comprises (1) a compound of the present invention, and (2) a pharmaceutically acceptable excipient, diluent, or carrier. **(page 8, lines 3-7; and Original Claim 55)**

In yet another embodiment of the present invention, a method for treating a disease, condition or disorder modulated by a cannabinoid receptor (preferably, a CB1 receptor) antagonists in animals that includes the step of administering to an animal in need of such treatment a therapeutically effective amount of a compound of the present invention (or a pharmaceutical composition thereof). **(page 8, line 15-19; page 33, lines 17-24; and Original Claims 59 and 64)**

Diseases, conditions, and/or disorders modulated by cannabinoid receptor antagonists include eating disorders (e.g., binge eating disorder, anorexia, and bulimia), weight loss or control (e.g., reduction in calorie or food intake, and/or appetite suppression), obesity, depression, atypical depression, bipolar disorders, psychoses, schizophrenia, behavioral addictions, suppression of reward-related behaviors (e.g., conditioned place avoidance, such as suppression of cocaine- and morphine-induced conditioned place preference), substance abuse, addictive disorders, impulsivity, alcoholism (e.g., alcohol abuse, addiction and/or dependence including treatment for abstinence, craving reduction and relapse prevention of alcohol intake), tobacco abuse (e.g., smoking addiction, cessation and/or dependence including treatment for craving reduction and relapse prevention of tobacco smoking), dementia (including memory loss, Alzheimer's disease, dementia of aging, vascular dementia, mild cognitive impairment, age-related cognitive decline, and mild neurocognitive disorder), sexual dysfunction in males (e.g., erectile difficulty), seizure disorders, epilepsy, inflammation, gastrointestinal disorders (e.g., dysfunction of gastrointestinal motility or intestinal propulsion), attention deficit disorder (ADD/ADHD), Parkinson's disease, and type II diabetes. **(page 8, line 20 through page 9, line 2; and page 33, line 25 – page 34, line 8)** In a preferred embodiment, the method is used in the treatment of weight loss, obesity, bulimia, ADD/ADHD, Parkinson's disease, dementia, alcoholism, and/or tobacco abuse. **(page 9, line 2-4; and Original Claims 63 and 68)**

The limitations of Claims 5, 6, 32 and 33 were incorporated into Claim 1 and Claims 44, 46, 50 and 52 were incorporated into Claim 42 (i.e., A is nitrogen, B is carbon, and X is a bond) in

an amendment received in the USPTO on June 30, 2005 in response to a restriction requirement mailed on June 10, 2005.

GROUNDS OF REJECTIONS TO BE REVIEWED ON APPEAL

I. The general issue on Appeal is whether the Examiner erred in rejecting Claims 1, 4, 8-11, 31, 35, 36, 42, 43, 49, 55, 59 and 64 under 35 U.S.C. §112, first paragraph, for non-enablement over the scope of the claims.

II. The general issue on Appeal is whether the Examiner erred in rejecting Claims 1, 4, 8-11, 31, 35, 36, 42, 43, 49, 55, 59 and 64 on the ground of non-statutory obviousness-type double patenting over Claims 1-23 of US Patent No. 7,230,024.

ARGUMENTS OF APPELLANTS

I. *Claims 1, 4, 8-11, 31, 35, 36, 42, 43, 49, 55, 59 and 64 have been finally rejected under 35 U.S.C. §112, first paragraph for non-enablement over the scope of the claims.*

The Examiner based the rejection on the reasons set forth in the Office Action mailed on mailed on August 4, 2008 and repeated in the Advisory Action mailed on September 4, 2008 which states that "in view of the art and the predictability in the art, applicants have not provided any examples with the R4 being a heterocyclic group such as piperidinyl, pyrrolidinyl or morpholin-4-yl. There are no tests done only some description of assays." Applicant would like to point out to the Examiner page 52, lines 25-26 of the specification, which clearly states "CB-1 binding activities of 4 nM and 2 nM were observed for Examples 1A-2 and 1A-3, respectively. Although the R^4 in both of these compounds are alkyl groups, it is important to note that it is unnecessary for an applicant to satisfy the "how-to-use" requirement of 35 USC § 112 for each member of a claimed group of compounds.

> "Early filing of an application with its disclosure of novel compounds which possess significant therapeutic use is to be encouraged. Requiring specific testing of the thousands of ... analogs encompassed by the present claim in order to satisfy the now-to-use requirement of §112 would delay disclosure and frustrate, rather than further, the interests of the public." *In re Bundy*, 209 USPQ 48, 52 (CCPA 1981).

Clearly, the binding data referred to above indicates that the compounds according to the invention are active. Even without data, however, the instant patent application, including any statement of utilities, must be taken as presumptively accurate. See in re Marzocchi, 169 USPQ 367, 369 (CCPA 1971), where it was stated:

> ""[A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with enabling requirement of the first paragraph of §112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support."

The burden is on the Examiner to come forth with evidence to establish a *prima facie* case. No specific factual evidence has been presented to establish a *prima facie* case pertaining to §112 which is relevant to the present invention. Instead, Examiner asserted that the fact that SR141716A (a known CB-1 antagonist) received an "approvable" letter from the FDA shows the unpredictability in the art. Clearly, the Examiner doesn't understand the meaning of an

"approvable" letter. Just because Sanofi received an "approvable" letter does not mean that the compound doesn't have utility. In fact, rimonabant (SR141716A) is approved in Europe and is currently being sold as an anti-obesity agent. In the more recent office action, Examiner goes on to assert that since fluphenazine (an approved drug for the treatment of psychotic disorders) and LDS both bind to the 5-HT6 receptor, LDS should be used to treat psychotics. Clearly, the Examiner doesn't understand the difference between an agonist and an antagonist. If a compound binds to a receptor, it has some utility if it mediates the activity of that receptor in some way (e.g., an agonist or an antagonist). However, just because a compound binds to a receptor does not indicate that all compounds that bind have the same utility. Clearly, if a compound acts as an agonist, it would not have the same properties as an antagonist. Consequently, Examiner's logic with respect to fluphenazine and LSD above is irrational.

Applicants used a known CB-1 antagonist (SR141716A) as a competitive test compound, thus Applicants have a reasonable expectation that the inventive compounds tested would have similar properties. The Examiner bears the burden of producing sufficient evidence that one of ordinary skill in the art would have reason to doubt the claimed utility of the invention. In the instant application, it is respectfully submitted that the Examiner has not overcome that burden, i.e., she has failed to supply any credible evidence that would cause one to reasonably doubt the utility of Applicant's invention. Applicants have not cited any incredible or unbelievable utilities in their specification or claims which could be questioned by the Examiner. The fact that several research efforts were initiated due to the teachings of SR141716A proves that those of skill in the art had sufficient confidence in the mechanism based on these teachings to invest in their own research. In fact, SR141716A served as a benchmark for those research efforts. The multitude of references cited in the IDS's of record clearly establish that compounds that bind to the CB-1 receptor have a variety of utilities. One skilled in the art of pharmaceuticals would know how to use the assays provided in the specification to determine whether a compound not only binds to a CB-1 receptor, but also whether it acts as an agonist, or antagonist /inverse agonist.

SR141716 is known to act as both an antagonist and inverse agonist at the CB-1 receptor and is often referred to as a CB-1 antagonist/inverse agonist. Applicant can rely on the fact that SR141716 was known to act as a CB-1 antagonist/inverse agonist with its associated uses as a reasonable basis for utility of their compounds as tested in similar assays (e.g., competitive antagonist assay). Examiner has provided no credible evidence to the contrary. Numerous authors have discussed the uses of CB-1 antagonists as anti-obesity agents as well as other

indications in the literature. See the numerous references cited in the previous IDS forms of record. As stated in MPEP 2107.03,

> "The applicant does not have to prove that a correlation exists between a particular activity and an asserted therapeutic use of a compound as a matter of statistical certainty, nor does he or she have to provide actual evidence of success in treating humans where such a utility is asserted. Instead, as the courts have repeatedly held, all that is required is a reasonable correlation between the activity and the asserted use. An applicant can establish a reasonable correlation by relying on statistically relevant data documenting the activity of a compound or composition, arguments or reasoning, documentary evidence (e.g., articles in scientific journals), or any combination thereof.

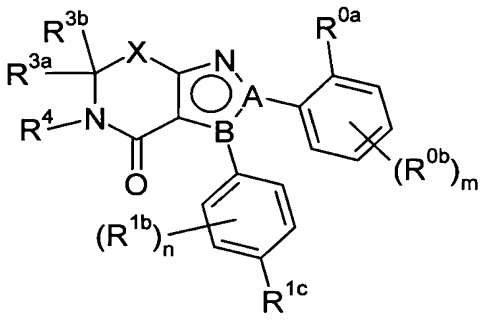
The MPEP also states that data generated using *in vitro* assays almost invariably will be sufficient to establish therapeutic or pharmacological utility for the compound, composition or process. Applicants respectfully submit that he has provided a reasonable correlation based on the numerous articles submitted in the IDS forms of record and the binding data submitted in the specification. Examiner has failed to provide any credible evidence contradicting this reasonable correlation.

Examiner has admitted on the record that the specification is enabling for compounds wherein R^1 and R^0 are aryl(phenyl) with halogen or methoxy substituents, or R^4 is an alkyl, halogen substituted alkyl or a cycloalkyl, which basically represents only those compound exemplified in the specification. However, Examiner is refusing to allow a reasonable genus surrounding the exemplified compounds which is contrary to established law. As part of the enablement requirement, it is well-established that one does not have to provide exemplification of every compound that falls within the scope of the claims. Clearly, it is well within the skill of the art to make compounds as presently claimed. Examiner has failed to provide any credible evidence to the contrary. Consequently, Applicants respectfully submit that the rejection is without merit and should be withdrawn.

II. *Claims 1, 4, 8-11, 31, 35, 36, 42, 43, 49, 55, 59 and 64 have been finally rejected on the ground of nonstatutory obviousness-type double patenting over Claims 1-23 of US Patent No. 7,230,024*.

The Examiner based the rejection on the reasons set forth in the Office Action mailed on mailed on August 4, 2008 and repeated in the Advisory Action mailed on September 4, 2008. Examiner's sole basis for the non-statutory double patenting rejection rests on her assertion that the core structure of the inventive compounds are positional isomers of the compounds disclosed in US 7,230,024. She asserts that "the order is the same just the attachment is in the

anticlockwise, instead of the clockwise, making them positional isomer" with no explanation of why this would be an obvious variation. Firstly, the inventive compounds are not mere positional isomers of those disclosed and claimed in US 7,230,024. Although the structures below would be considered structural isomers, they are not positional isomers. Clearly, changing the orientation of the core is much more than just moving the point of attachment of a single substituent. If one compares the two Formula (III) structures below, one can easily see that access to the carbonyl is hindered in one of the structures but not in the other one. In both the Formula (III) and Formula (IV) structures, the closeness of the R^{3a} and R^{3b} substituents on one orientation would have more influence on the phenyl group than the other orientation. This could easily affect the binding of the compound to a receptor.



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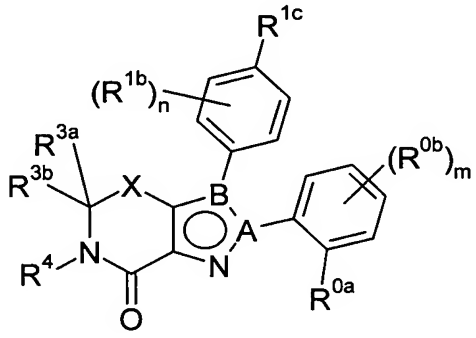

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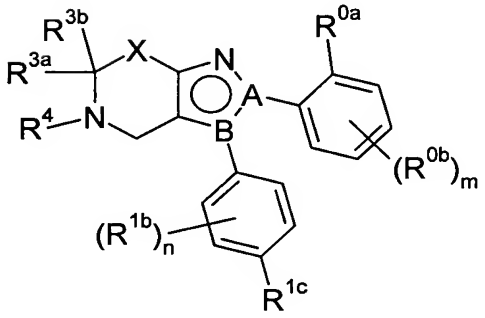
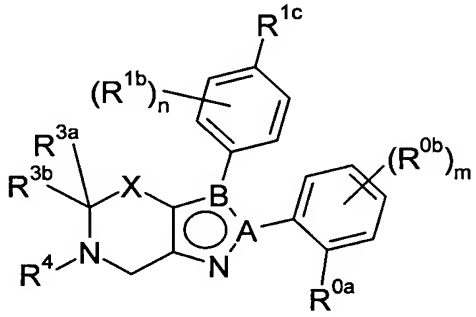


(IV)

Compounds of the present invention



(IV)

Compounds of US 7,230,024

In all of the compounds above, X is a bond, A is nitrogen and B is carbon.

It is well known that binding to a receptor can be influenced by the orientation of the groups on the compound; consequently, one would not be able to predict with any certainty that such a compound would work until it was made and tested. Therefore, it would not be obvious that the compounds of the present invention would even bind to the CB-1 receptor let alone act as a

CB-1 antagonist/inverse agonist based on the compounds disclosed and claimed in US 7,230,024.

In *Takeda Chemical vs. Alphapharm* (Fed Cir., No. 06-1329, 2007), the court states that "in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound." The court found that because there was no motivation in the prior art for selecting the earlier compound as the lead compound for research, the burden for proving a prima facie case of obviousness based on a structurally similar compound was not met. The Examiner implies that "positional" isomers of the prior art compounds would have similar properties and would therefore it would be obvious to make them. This is clearly contrary to the findings of the Takeda court.

> "Our case law concerning prima facie obviousness of structurally similar compounds is well-established. We have held that "structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a prima facie case of obviousness." Dillion, 919 F.2d at 691. In addition to structural similarity between the compounds, ***a prima facie case of obviousness also requires a showing of "adequate support in the prior art" for the change in structure***. In re Grabiak, 769 F.2d 729, 731-32 (Fed Cir. 1985).
>
> We elaborated on this requirement in the case of In re Deuel, 51 F.3d 1552, 1558 (Fed. Cir. 1995), where we stated that "[n]ormally a prima facie case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound." That is so because close or established "[s]tructural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds." Id. A known compound may suggest its homolog, analog, or isomer because such compounds "often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties." Id. We clarified, however, that in order find a prima facie case of unpatentability in such instances, ***a showing that the "prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention" was also required***. Id. (citing In re Jones, 958 F.2d 247 (Fed Cir. 1992), 919 R.2d 688; Grabiak, 769 F.2d 729; In re Lalu, 747 F.2d 703 (Fed Cir. 1984)).
>
> That test for prima facie obviousness for chemical compounds is consistent with the legal principles enunciated in KSR. While the KSR Court rejected a rigid application of the teaching, suggestion, or motivation ("TSM") test in an obviousness inquiry, the Court acknowledged the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant filed to combine the elements in the way the claimed new invention does" in an obviousness determination. KSR, 127 S.Ct. at 1731. Moreover, the Court indicated that there is "no necessary inconsistency between the idea underlying the TSM test and the Graham analysis." Id. As long as the test is not

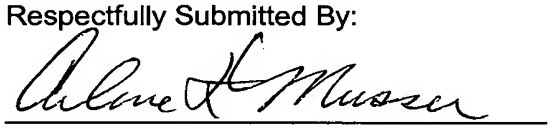
> applied as a "rigid and mandatory" formula, that test can provide "helpful insight" to an obviousness inquiry. Id. Thus, ***in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound.***" (Emphasis added) *Takeda Chemical vs. Alphapharm* (Fed Cir., No. 06-1329, 2007)

The Examiner provided no evidence that there existed a reason, based on what was known at the time of the invention, to make the chemical modifications necessary to achieve the claimed compounds. Instead, the Examiner merely asserts that positional isomers are not patentable. This is clearly contrary to the case law outlined above. Therefore, Examiner has failed to meet her burden for showing a prima facie case of obviousness in support of the non-statutory double patenting rejection.

Conclusion

Based on the arguments presented above, Applicant respectfully submits that Claims 1, 4, 8-11, 31, 35, 36, 42, 43, 49, 55, 59 and 64 are in condition for allowance.

Respectfully Submitted By:



September 15, 2008

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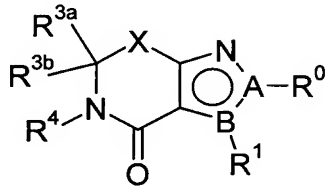
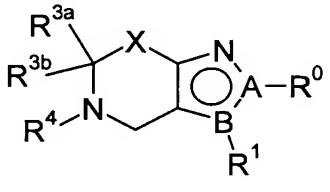
CLAIMS APPENDIX

1(previously presented). A compound of Formula (I) or (II)



(I)



(II)

wherein

A is nitrogen and B is carbon;

R^0 is a phenyl substituted with 1 to 3 substituents independently selected from the group consisting of halo, $(C_1$-$C_4)$alkoxy, halo-substituted $(C_1$-$C_4)$alkyl, and cyano;

R^1 is a phenyl substituted with 1 to 3 substituents independently selected from the group consisting of halo, $(C_1$-$C_4)$alkoxy, halo-substituted $(C_1$-$C_4)$alkyl, and cyano;

X is a bond;

R^{3a} and R^{3b} are each independently hydrogen, $(C_1$-$C_4)$alkyl, or halo-substituted $(C_1$-$C_4)$alkyl; and

R^4 is $(C_1$-$C_8)$alkyl, halo-substituted $(C_1$-$C_8)$alkyl, cyclopentyl, cyclohexyl, piperidin-1-yl, pyrrolidin-1-yl, or morpholin-4-yl;

provided that when the compound is a compound of Formula (II), R^{3a} and R^{3b} are not both hydrogen.

2-3(cancelled).

4(previously presented). The compound of Claim 1 wherein said compound is a compound of Formula (I); or a pharmaceutically acceptable salt thereof.

5-7(cancelled).

8(previously presented). The compound of Claim 4 wherein R^0 and R^1 are each independently a phenyl substituted with 1 to 2 substituents independently selected from the

group consisting of chloro, fluoro, (C_1-C_4)alkoxy, fluoro-substituted (C_1-C_4)alkyl), and cyano; or a pharmaceutically acceptable salt thereof.

9(previously presented). The compound of Claim 8 wherein R^0 is 2-chlorophenyl, 2-fluorophenyl, 2,4-dichlorophenyl, 2-fluoro-4-chlorophenyl, 2-chloro-4-fluorophenyl, or 2,4-difluorophenyl; and R^1 is 4-chlorophenyl, 4-cyanophenyl, or 4-fluorophenyl; or a pharmaceutically acceptable salt thereof.

10(previously presented). The compound of Claim 4 selected from the group consisting of

2-(2-chloro-phenyl)-5-isopropyl-3-(4-methoxy-phenyl)-5,6-dihydro-2H-pyrrolo[3,4-c]pyrazol-4-one;

2-(2-chloro-phenyl)-5-isopropyl-3-(4-cyano-phenyl)-5,6-dihydro-2H-pyrrolo[3,4-c]pyrazol-4-one;

2-(2-chloro-phenyl)-5-isopropyl-3-(4-chloro-phenyl)-5,6-dihydro-2H-pyrrolo[3,4-c]pyrazol-4-one;

3-(4-chloro-phenyl)-2-(2-chloro-phenyl)-5-(2,2,2-trifluoro-ethyl)-5,6-dihydro-2H-pyrrolo[3,4-c]pyrazol-4-one;

3-(4-chloro-phenyl)-2-(2-chloro-phenyl)-5-cyclohexyl-5,6-dihydro-2H-pyrrolo[3,4-c]pyrazol-4-one;

3-(4-chloro-phenyl)-2-(2,4-dichloro-phenyl)-5-isopropyl-5,6-dihydro-2H-pyrrolo[3,4-c]pyrazol-4-one;

3-(4-chloro-phenyl)-2-(2,4-dichloro-phenyl)-5-(2,2,2-trifluoro-ethyl)-5,6-dihydro-2H-pyrrolo[3,4-c]pyrazol-4-one;

3-(4-chloro-phenyl)-5-cyclohexyl-2-(2,4-dichloro-phenyl)-5,6-dihydro-2H-pyrrolo[3,4-c]pyrazol-4-one;

3-(4-chloro-phenyl)-2-(3-chloro-phenyl)-5-isopropyl-5,6-dihydro-2H-pyrrolo[3,4-c]pyrazol-4-one;

3-(4-cyano-phenyl)-2-(3-chloro-phenyl)-5-(2,2,2-trifluoro-ethyl)-5,6-dihydro-2H-pyrrolo[3,4-c]pyrazol-4-one;

3-(4-chloro-phenyl)-2-(3-chloro-phenyl)-5-(2,2,2-trifluoro-ethyl)-5,6-dihydro-2H-pyrrolo[3,4-c]pyrazol-4-one; and

3-(4-chloro-phenyl)-2-(3-chloro-phenyl)-5-cyclohexyl-5,6-dihydro-2H-pyrrolo[3,4-c]pyrazol-4-one; or a pharmaceutically acceptable salt thereof.

11(previously presented). The compound of Claim 10 selected from the group consisting of

2-(2-chloro-phenyl)-5-isopropyl-3-(4-cyano-phenyl)-5,6-dihydro-2H-pyrrolo[3,4-c]pyrazol-4-one;

2-(2-chloro-phenyl)-5-isopropyl-3-(4-chloro-phenyl)-5,6-dihydro-2H-pyrrolo[3,4-c]pyrazol-4-one; and

3-(4-chloro-phenyl)-2-(2-chloro-phenyl)-5-(2,2,2-trifluoro-ethyl)-5,6-dihydro-2H-pyrrolo[3,4-c]pyrazol-4-one; or a pharmaceutically acceptable salt thereof.

12-30(cancelled).

31(previously presented). The compound of Claim 1 wherein said compound is a compound of Formula (II); or a pharmaceutically acceptable salt thereof.

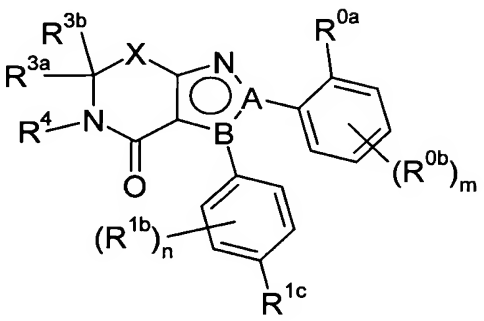
32-34(cancelled).

35(previously presented). The compound of Claim 31 wherein R^0 and R^1 are each independently a phenyl substituted with 1 to 2 substituents independently selected from the group consisting of chloro, fluoro, $(C_1$-$C_4)$alkoxy, fluoro-substituted $(C_1$-$C_4)$alkyl), and cyano; or a pharmaceutically acceptable salt thereof.

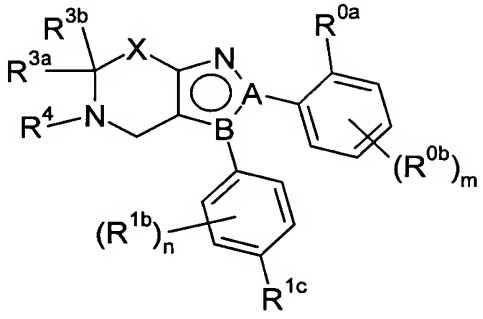
36(previously presented). The compound of Claim 35 wherein R^0 is 2-chlorophenyl, 2-fluorophenyl, 2,4-dichlorophenyl, 2-fluoro-4-chlorophenyl, 2-chloro-4-fluorophenyl, or 2,4-difluorophenyl; and R^1 is 4-chlorophenyl, 4-cyanophenyl, or 4-fluorophenyl; or a pharmaceutically acceptable salt thereof.

37-41(cancelled).

42(previously presented). A compound of Formula (III) or (IV)



(III)



(IV)

wherein

A is nitrogen and B is carbon;

R^{0a}, R^{0b}, R^{1b}, and R^{1c} are each independently halo, (C_1-C_4)alkoxy, (C_1-C_4)alkyl, halo-substituted (C_1-C_4)alkyl, or cyano;

n and m are each independently 0, 1 or 2;

X is a bond;

R^{3a} and R^{3b} are each independently hydrogen, (C_1-C_4)alkyl, or halo-substituted (C_1-C_4)alkyl; and

R^4 is (C_1-C_8)alkyl, halo-substituted (C_1-C_8)alkyl, cyclopentyl, cyclohexyl, piperidin-1-yl, pyrrolidin-1-yl, or morpholin-4-yl; or

a pharmaceutically acceptable salt thereof:

provided that when said compound is a compound of Formula (IV), R^{3a} and R^{3b} are not both hydrogen.

43(previously presented). The compound of Claim 42 wherein said compound is a compound of Formula (III); or a pharmaceutically acceptable salt thereof.

44-48(cancelled).

49(previously presented). The compound of Claim 42 wherein said compound is a compound of Formula (IV); or a pharmaceutically acceptable salt thereof.

50-54(cancelled).

55(previously presented). A pharmaceutical composition comprising (1) a compound of Claim 1, or said salt; and (2) a pharmaceutically acceptable excipient, diluent, or carrier.

56-58 (cancelled).

59(previously presented). A method for treating obesity comprising the step of administering to an animal in need of such treatment a therapeutically effective amount of a compound of Claim 1; or a pharmaceutically acceptable salt thereof.

60-63(cancelled).

64(previously presented). A method for treating obesity comprising the step of administering a pharmaceutical composition of Claim 55.

65–73 (cancelled).

EVIDENCE APPENDIX

No evidence was submitted during the prosecution of this application.

RELATED PROCEEDINGS APPENDIX

No related co-pending Interferences or Appeals in the U.S. Patent & Trademark Office.